Aetna considers eculizumab (Soliris) medically necessary for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis when all of the following criteria are met:

- Documented diagnosis of PNH, with flow cytometric confirmation of at least 10% PNH type III red cells or greater than 50% of glycosylphosphatidylinositol-anchored proteins (GPI-AP)-deficient poly-morphonuclear cells (PMNs); and
- Member has been vaccinated against meningococcal infection (at least 2 weeks prior to eculizumab treatment, if not previously vaccinated); and
- Member does not meet diagnostic criteria for severe aplastic anemia (see Appendix); and
- Member meets either of the following criteria:
  - Member is transfusion-dependent (i.e., has at least 1 transfusion in the 24 months prior to initiation of eculizumab due to documented hemoglobin less than 7 g/dL in persons without anemic symptoms or less than 9 g/dL in persons with symptoms from anemia) prior to initiation of eculizumab treatment; or
  - Member has a documented history of major adverse vascular events from thromboembolism (see Appendix).

Aetna considers eculizumab medically necessary for the treatment of atypical hemolytic uremic syndrome without serious unresolved Neisseria meningitidis infection.

These products are NOT covered for members with the following criteria:

- Use not approved by the FDA; AND

The use is unapproved and not supported by the literature or evidence as an accepted off-label use.

- Age-related macular degeneration
- Antibody-mediated rejection
- Anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis
Anti-phospholipid antibody syndrome
Autoimmune hemolytic anemia
C3 glomerulopathy
Deposit disease/C3 glomerulonephritis
Guillain-Barre syndrome
Hemolytic cold agglutinin disease
IgA nephropathy
Inflammatory myositis (e.g., dermatomyositis and polymyositis)
Multi-focal motor neuropathy
Myasthenia gravis
Neuromyelitis optica (Devic's disease)
Non-exudative (dry) macular degeneration
Preeclampsia with hemolysis, elevated liver enzymes and low platelets (HELP) syndrome
Shiga toxin E. coli-related hemolytic uremic syndrome (STEC-HUS)
Systemic lupus erythematosus
Thrombotic thrombocytopenic purpura (TTP)
Transverse myelitis

See CPB 0634 - Non-myeloablative Bone Marrow/Peripheral Stem Cell Transplantation (Mini-Allograft / Reduced Intensity Conditioning Transplant).

Background

Paroxysmal nocturnal hemoglobinuria (PNH), a rare form of hemolytic anemia, is caused by a somatic mutation of the X-linked phosphatidylinositol glycan class A (PIGA) gene, which results in the absence of the glycosylphosphatidylinositol-linked proteins necessary to protect cells from complement-mediated lysis. Prior to 1990, diagnosis of PNH was made by means of complement-based tests. In the past 10 years, flow cytometry has become the gold standard test as it has increased sensitivity to detect small clones, ability to measure clonal size, and is not affected by blood transfusions (Preis et al, 2014). Uncontrolled complement activity in PNH leads to systemic complications, principally through intravascular hemolysis and platelet activation (Hill et al, 2013). The primary clinical manifestations of PNH entail intra-vascular hemolytic anemia, thrombosis in vessels, and bone marrow failure. Inactivating mutations appear only in a proportion of cells (PNH cells) and this proportion can vary among patients. Treatment of PNH has largely been supportive care measures including anti-coagulation, folic acid supplementation, hydration, and red blood cell (RBC) transfusion until the development of eculizumab (Zareba, 2007; Madkaikar et al, 2009).

On March 16, 2007, eculizumab (Soliris; Alexion Pharmaceuticals, Inc., Cheshire, CT), received accelerated approval as an orphan drug by the Food and Drug Administration (FDA) for the treatment of patients with PNH to reduce hemolysis. Eculizumab is a recombinant humanized monoclonal antibody that works by binding to complement protein C5, inhibiting its enzymatic cleavage, blocking formation of the terminal complement complex, and thus preventing red cell lysis. The FDA approval of eculizumab was based mainly on a randomized, double-blind, placebo-controlled, clinical trial in 87 RBC transfusion-dependent adult PNH patients, with supportive evidence from two observational studies: (i) a phase II pilot study involving 11 PNH transfusion-dependent
patients, and (ii) a 52-week, open-label, non-placebo-controlled, single-arm study in 96 PNH patients (Dmytrijuk et al, 2008).

Pivotal clinical studies of eculizumab in PNH were performed in persons with PNH who were transfusion-dependent, representing a subgroup of patients in the most severe end of the disease spectrum. The European Medicines Agency has stated that "there is only experience in the treatment of patients with previous history of transfusions." Although estimates of the proportion of persons with PNH with disease severity similar to study subjects have varied (15 % to 40 %) (Kar, 2007; Connock et al, 2008; Scottish Medicines Consortium, 2007; London New Drugs Group, 2008), this subgroup represents a minority of persons with PNH. In a submission by the manufacturer of eculizumab to the National Health Service, the manufacturer anticipated that eculizumab would be reserved for use in the most severely affected patients (estimated to be 15 % of PHN patients) (Alexion Pharma, 2008).

A phase II pilot study examined the effect of eculizumab on transfusion requirements and hemolysis. Adult patients with a history of PNH for at least 6 months who had received at least 4 red cell transfusions in the preceding 12 months were eligible. Eleven transfusion-dependent patients with PNH received transfusions of eculizumab (600 mg) every week for 4 weeks, followed 1 week later by a 900-mg does and then by 900-mg every other week through week 12. The primary endpoint of this study was hemolysis as measured by LDH. The mean transfusion rate decreased from 2.1 units per patient per month to 0.6 units per patient per month. Mean lactate dehyhdrogenase (LDH) levels (a measure of hemolysis) decreased from 3,111 IU/L before treatment to 594 IU/L during treatment (p = 0.002).

In the pivotal randomized controlled clinical study (Transfusion Reduction Efficacy and Safety Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria [TRIUMPH]), Hillmen and colleagues (2006) enrolled 87 PNH patients who had received at least 4 transfusions in the prior 12 months, had a flow cytometric confirmation of at least 10 % PNH cells, and platelet counts of at least 100,000/microliter. All subjects received meningococcal vaccination prior to treatment, and were randomized to receive either eculizumab (n = 43) or placebo (n = 44). Prior to randomization, all patients underwent an initial observation period to confirm the need for transfusion of RBCs and to identify the hemoglobin (Hb) concentration (the "set-point"), which would define each patient’s Hb stabilization and transfusion outcomes. Patients who did not need a red cell transfusion during the 3-month observation were not eligible for randomization. The Hb set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Endpoints related to hemolysis included the numbers of patients achieving Hb stabilization, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of Hb stabilization, a patient had to maintain a Hb concentration above the Hb set-point and avoid any transfusion of RBCs for the entire 26-week period. Hemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH RBCs was monitored by flow cytometry. Patients receiving anti-coagulants and systemic corticosteroids at baseline continued these medications.

The 2 primary endpoints of the study were hemoglobin stabilization and the number of units of packed red blood cells transfused. Patients treated with eculizumab had significantly reduced hemolysis (p < 0.001) resulting in improvements in anemia as indicated by increased Hb stabilization and reduced need for RBC transfusions compared
Eculizumab (Soliris)

Eculizumab (Soliris) increased the baseline score for fatigue by 6.4 points on the FACIT-Fatigue instrument (score range 0 to 52), where a change of 3 or more points is the minimal change that is considered clinically significant. Patients also reported improvements in health-related quality of life. No thrombotic episodes were seen in the eculizumab group (21 of 43 patients in this group were on anti-coagulant drugs), whereas one thrombotic episode was reported in the placebo group (11 of 44 in this group were on anti-coagulant drugs). Because changes in medications were not permitted, the impact of eculizumab on supportive therapy is not known.

In a 3rd, open-label study (Safety in Hemolytic PNH Patients Treated with Eculizumab: A Multi-centre Open-label Research Design Study [SHEPHERD]), Brodsky et al (2008) examined the safety and effectiveness of eculizumab in 97 subjects who had received at least 1 transfusion in the prior 24 months and with at least 30,000 platelets/microliter. A PNH type III RBC proportion of 10% or more as assessed by flow cytometry and LDH levels of 1.5 times or more the upper limit of the normal range were also required. All subjects received meningococcal vaccination prior to receiving an open-label, non-placebo-controlled, 52-week. Concomitant medications included anti-thrombotic agents in 63 % of the patients and systemic corticosteroids in 40 % of the patients. Overall, 96 of the 97 enrolled patients completed the study (1 patient died following a thrombotic event). Efficacy outcomes for SHEPHERD were similar to those reported in both the phase II pilot study and TRIUMPH with transfusion-dependent stabilization of hemoglobin concentration, reduction in red-cell transfusion requirement, reduction in intravascular hemolysis (on the basis of a reduction in serum LDH concentration) and improvement in quality of life, particularly fatigue. A reduction in intra-vascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBCs transfusion and less fatigue. Two patients with a history of thrombosis had a thrombotic event during the study.

All patients who participated in the 3 clinical trials described above were eligible for the extension study in which patients continued to receive eculizumab. Of 195 eligible patients, 187 enrolled in this long-term extension study which lasted 104 weeks. All patients sustained a reduction in intravascular hemolysis over a total eculizumab exposure time ranging from 10 to 54 months. There were fewer thrombotic events with eculizumab treatment than during the same period of time prior to treatment. However, the majority of patients received concomitant anticoagulants; the effects of anti-coagulant withdrawal during eculizumab therapy was not studied.

Despite differences in patient selection criteria in the TRIUMPH study and the SHEPHERD study, subjects in each study were similar in representing a subgroup of subjects at the most severe end of the spectrum of PNH disease. In a recent review of eculizumab for PNH published in the Lancet, Parker (2009) observed that although entry criteria for the open-label SHEPHERD study were different from those of the pivotal randomized controlled TRIUMPH study, no detailed statistical comparison between the demographic and baseline characteristics of the population of the 2 studies was presented in these publications. Therefore, the extent of the difference could not be discerned from the data presented in these publications. Parker noted, however, that data in a subsequent report showed considerable overlap in the 2 populations, including platelet count (162,000 per microliter for SHEPHERD versus 136,000 per microliter for SHEPHERD), size of PNH granulocyte clone (95% for TRIUMPH versus 96% for
SHEPHERD), median proportion of type III red blood cell clones at baseline (greater than 30% in TRIUMPH and SHEPHERD), and median LDH at baseline (2,200 U/L in TRIUMPH and 2,051 U/L for SHEPHERD).

Paroxysmal nocturnal hemoglobinuria is associated with a marked increase in venous thrombosis in the hepatic, other intra-abdominal, and peripheral veins. While this propensity to thrombosis is not well understood, it is thought to be due to activation of complement on the platelet surface, which stimulates removal of complement complexes by vesiculation; the resulting circulating microparticles are rich in phosphatidylserine and are highly thrombogenic (Rosse, 2007; Rosse, 2010). The risk of thrombosis appears to be significantly related to the size of the PNH clone. In 2 series, almost all patients developing thrombosis had more than 50% or more than 61% PNH granulocytes (Nishimura et al, 2004; Moyo et al, 2004; and Rosse, 2010).

There is a lack of reliable evidence of the effect of eculizumab on survival or on the incidence of thromboembolic events (CADTH, 2010). No evidence on the effect of eculizumab on thromboembolism was submitted to regulatory authorities. Studies that have used "suboptimal" experimental design suggest that eculizumab might ameliorate the thrombophilia of PNH (Parker et al, 2007; Parker, 2009). Although these studies suggest a role for eculizumab in the management of thromboembolic complications of PNH, "this issue would be best addressed by a prospective, randomized study" (Parker et al, 2007).

To assess the rate of thromboembolic events prior to and following initiation of eculizumab, Hillman et al (2007) compared retrospectively collected data to observational data in patients patients from the original pilot trial, TRIUMPH, SHEPHERD and the Phase IIib extension study. Thromboembolism events were assessed in the major adverse vascular event (MAVE) criteria (see Appendix). The principal investigators were responsible for the description, location, method of diagnosis, date of diagnosis, and date of resolution of each MAVE. Events that antedated treatment with eculizumab were identified retrospectively from the period starting from the earlier of either the date of diagnosis of PNH or the date of the first thrombotic event to the time of the first eculizumab treatment. The study found a relative reduction of 85% in thromboembolism event rate during eculizumab treatment. In a critique of the study by Hillman et al, Parker noted that, with this method of comparing retrospective data with observational data, Hillman et al noted a substantial reduction in thromboembolic events in patients treated with eculizumab. For example, the rate of thromboembolism was 7.37 events per 100 patient years before eculizumab treatment compared with 1.07 events per 100 patient years during treatment (p < 0.001), and thromboembolic events were reduced from 39 before treatment to 3 during eculizumab treatment (p < 0.001). No data were provided to determine whether the magnitude of reduction in thromboembolic events observed during eculizumab treatment is the same or different across different types of thromboembolic events. There are also no direct survival data available for eculizumab.

Parker stated that the results of the study by Hillman et al suggest that eculizumab ameliorates the thrombophilia of PNH, "but the study design makes assessment of the effect of treatment nebulous." Parker stated that the major concerns are: (i) the use of MAVE criteria that did not require uniform documentation to characterize the thromboembolic event; and (ii) the use of retrospective data to estimate the rate of thrombosis before starting treatment. This clinical study used non-uniform documentation of thromboembolic events and compared retrospective data with observational data.
Although this study suggested that eculizumab ameliorates risk of thromboembolic complications, "interpretation of these findings is debatable because of suboptimal experimental design."

Parker observed that, in the only part of the study that was randomized and included a placebo group (TRIUMPH), one thromboembolic event occurred in the placebo group (11 of 44 patients were on anticoagulant drugs) and no thromboembolic events occurred in the eculizumab-treated group (21 of 43 patients were anticoagulated). Parker observed that a large difference in the pretreatment thromboembolic rate was also seen among the treatment groups. For example, in the placebo group of TRIUMPH, the thromboembolic event rate was 2.34 per 100 patient years, versus a thromboembolic event rate of 12.67 per 100 patient years for SHEPHERD. Parker noted that these differences do not seem to be due to differences in baseline characteristics of the patients because the PNH clone sizes were equivalent. A high rate of pre-treatment thromboembolic events (10.31 per 100 patient years) was reported in patients treated with anti-thrombotic drugs in the Hillman study, whereas complete protection against thromboembolism in patients with PNH treated with warfarin was previously reported in an earlier study coauthored by Hillmen (Hall et al, 2003), where data were also collected retrospectively.

A review by the Canadian Agency for Drugs and Technologies in Health (2010) concurred that although this study suggests a significant reduction in thrombotic event rates, "limitations associated with retrospective data collection and non-randomized studies limit the scientific validity of these data."

An assessment by the All Wales Medicines Strategy Group (2009) noted that the rates of baseline thrombosis in the eculizumab trials was substantially higher than the rate in patients at presentation in one of the natural history studies presented to the group by the manufacturer of eculizumab. The group noted that although a significant proportion of subjects in these clinical studies received anticoagulants, it is not clear what proportion of patients who received anti-coagulants achieved adequate anticoagulation (e.g., INR levels within therapeutic range) either prior to initiation or eculizumab or during eculizumab treatment. Thus, it is not known whether improvements in thromboembolic event rates following eculizumab treatment may have been due to improved use of anti-coagulation.

In a post-hoc analysis of the extension study, eculizumab treatment was associated with a significant increase in the likelihood of improvement and prevention of worsening of kidney function (Hillmen et al, 2010). This is an analysis of data from studies that were not designed to assess the impact of eculizumab on renal function; thus, this analysis has limitations similar to the previously described post-hoc analysis of the association of eculizumab with thrombosis.

Hill, et al. (2010) investigated the effect of eculizumab on NO depletion, dyspnea and measures of pulmonary hypertension. This study was carried out with patients from the TRIUMPH trial only. Treatment with eculizumab significantly reduced NO depletion, dyspnea and decreased the proportion of patients with elevated pro-brain naturetic peptide (proBNP).

Most of the published literature regarding the use of eculizumab in patients with PNH has been derived from studies of 187 patients that were enrolled in the clinical trials that lead to FDA approval. To date, few studies have evaluated eculizumab outside the context of a clinical trial (Varela & Brodsky, 2013).
Kelly, et al. (2010) evaluated 79 consecutive patients treated with eculizumab in the UK between May 2002 and July 2010. Of the 79 patients, 34 were enrolled in one of the original clinical trials. Mean LDH at the initiation of treatment was 2872 U/L, mean PNH RBC clone size was 34%, mean PNH granulocyte clone size was 96.4%, and the mean number of units of PRBCs transfused within the 12 months prior to the study was 19.9. The authors reported that the survival of patients treated with eculizumab was not different from age- and sex-matched normal controls (P = .46) but was significantly better than 30 similar patients managed before eculizumab (P = .030).

Dezen, et al. (2013) reported on a retrospective, single center study that evaluated the response of 30 patients with PNH to treatment with eculizumab. Of 73 patients diagnosed with a PNH clone at Johns Hopkins University, 30 were treated with eculizumab and were the subjects of this study. Of note, out of these 30 patients, five were enrolled on the TRIUMPH or SHEPHERD trial. Mean LDH at the initiation of treatment was 1489 IU/L, mean PNH RBC clone size was 37.5%, mean PNH granulocyte clone size was 86.5%, and mean Hgb was 8.6 g/dL. Over 863 patient-months of eculizumab treatment, four patients had a complete response, 16 had a partial response, and 10 had a suboptimal response.

A number of authorities have concluded that treatment with eculizumab is not appropriate for all patients with PNH (Willacy, 2009; Parker, 2009; Parker, 2011). Parker (2009) has stated that, due to the heterogenous nature of PNH, "treatment with eculizumab is not appropriate for all patients with PNH." Parker explained that the extent to which the abnormal PNH clone expands varies widely among patients. Patients with a small number of PNH clonal cells have few symptoms and do not need PNH-specific treatment. In addition, patients with hypoplastic PNH, characterized by moderate to severe cytopenias and hypoplastic bone marrow, are less likely to respond to eculizumab, because bone marrow suppression, rather than complement-mediated hemolysis is the major mechanism of anemia; these patients are likely to respond to immunosuppressive therapy.

The European Medicines Agency concluded that "[e]vidence of clinical benefit of Soliris in patients with PNH is limited to patients with history of transfusions."

Brodsy (2010) commented that the only effective therapies for paroxysmal nocturnal hemoglobinuria are allogeneic bone marrow transplantation and inhibition of terminal complement with eculizumab. However, eculizumab does not improve bone marrow function and is not very effective for aplastic anemia/PNH. The author noted, moreover, that eculizumab is expensive, does not eradicate the PNH clone, and must be given lifelong; thus, it is best reserved for patients with classical paroxysmal nocturnal hemoglobinuria.

Brodsy (2009) stated that patients with classic PNH have signs and symptoms of intravascular hemolysis. These patients tend to have a normocellular to hypercellular bone marrow with erythroid hyperplasia, an elevated reticulocyte count, a large population of PNH cells (usually > 60% PNH granulocytes) and a lactic dehydrogenase (LDH) that is 2 to 10 times the upper limit of normal. Hemoglobinuria, smooth muscle dystonias (eg, esophageal spasm and erectile dysfunction), severe fatigue, and thrombosis are common in patients with classic PNH. Patients with small PNH clones in the setting of bone marrow failure probably represent bone marrow failure that is immune mediated, and immunosuppressive therapy is probably the most effective therapy in these patients.
An open-label, prospective 12-week phase II study (AEGIS) evaluated the effectiveness of eculizumab in reducing hemolysis (primary endpoint) in 29 Japanese patients with PNH, with enrollment criteria similar to previously published pivotal studies (Kanakura et al, 2011). Adults and adolescents were enrolled in the study if they had been diagnosed with PNH for at least 6 months and had a PNH RBC clone size of at least 10%, lactate dehydrogenase (LDH) levels >1.5 times the upper limit of normal (240 U/L), a platelet count >30 x 10^9/L, and a neutrophil count of greater than 500/µL. Patients were to have received or could have benefited from at least one RBC transfusion over the past 2 years. The mean PNH RBC clone size at initiation of the study was 43.6%, the mean LDH was 1827.6 U/L, the mean granulocyte clone size was 91.7%, the mean hemoglobin was 8 g/dL, and the median number of PRBCs transfused within the previous 12 months was 14. The investigators reported an 87% reduction in hemolysis and subsequent improvement in anemia with eculizumab. The long-term efficacy and safety of eculizumab was assessed in a 2-year extension to the AEGIS study (Kanakura et al., 2013). The investigators reported that eculizumab treatment led to an immediate and sustained reduction in intravascular hemolysis and red blood cell transfusions compared with baseline levels. There were no reports of thromboembolism during eculizumab treatment.

Hillmen et al (2013) reported on the long-term safety and efficacy of eculizumab in patients with hemolytic PNH who had participated in one of the three prospective parent trials: the Phase II pilot study and its extensions, the Phase III TRIUMPH or the Phase III SHEPHERD study. At the end of these initial studies, 187 of the 195 patients enrolled in an open-label extension study. All patients had a minimum of 10% PNH red blood cells at enrollment in the parent trials. Mean baseline hemoglobin in subjects was 9.37 g/dL, and mean LDH was 2229 U/L. All three parent trials employed the same dosing regimen: 600-mg infusions of eculizumab every week for 4 weeks, followed 1 week later by a single 900-mg dose, and then a maintenance dose of 900 mg every 14 (±2) days until the end of the study. In the extension study patients continued to receive the maintenance dose of eculizumab. The entire period of eculizumab administration across the parent and extension trials was 66 months, although a 36-month cut-off was used for safety and efficacy assessments to ensure that there were a sufficient number of patients for robust statistical analysis. The median eculizumab treatment duration was 30·3 months, with a maximum duration of 66 months. All patients showed a rapid decrease from baseline in serum LDH. This decrease was maintained with sustained eculizumab treatment; the median LDH value at 36 months was 279 U/L (range: 88–1417 U/L), a relative reduction from baseline of 86·9%. The percentage of patients achieving transfusion independence was 82·1% (64 of 78) by the last 6 months of treatment, compared with only 8·2% (16 of 195) in the 6 months prior to the start of treatment, a relative increase of 90.0%. Fourteen of 78 patients (17·9%) continued to require transfusions between months 30 and 36. The number of units of PRBCs transfused over the course of the study significantly decreased from a mean of 11·2 units in the 6 months prior to starting eculizumab to 3·5 units between months 30 and 36 (P = 0·0001). The percentage of patients free from TEs increased from 67·7% before treatment to 96·4% during treatment. Eighty-four patients in this study received concomitant anticoagulant therapy. The percentage of patients showing improvement, worsening or no change in chronic kidney disease was 44·8%, 6·9% and 48·3% respectively, at 36 months. Four patient deaths were reported, all unrelated to treatment, resulting in a 3-year survival estimate of 97·6%. Although nearly all patients reported at least one adverse event, discontinuation from treatment due to a nonfatal adverse event was seen in only five patients over the entire period of study.
Overall benefits of eculizumab in PNH have been estimated; using a Markov model, Coyle, et al. (2014) estimated that treatment of PNH with eculizumab is associated with 1.13 greater life years and 2.45 more quality adjusted life years (QALYs) per person than current standard of care.

A systematic review of evidence for eculizumab by the Institute for Clinical Effectiveness and Health Policy (Pichon Riviere et al, 2011) concluded that "the available evidence shows that eculizumab is effective in reducing complement-mediated hemolysis", but that "the evidence is not very strong since there is no CRCT [controlled randomized clinical trials] conducted on prevention of thrombotic events." The assessment stated that "it has not been determined if eculizumab therapy increases survival of PNH patients yet." The assessment noted that, "although some private insurance companies in the United States give coverage to certain patients, most health systems in different countries do not cover it due to its high costs and because it provides marginal benefits when compared with standard care for PNH."

Varela and Brodsky (2013) stated that the severity of symptoms is variable among patients diagnosed with PNH and not all patients require treatment. The authors state there are no clear guidelines for the use of eculizumab, but that it should not be routinely administered to patients who are minimally symptomatic or whose PNH clone size is very small. Given that eculizumab is expensive, does not eradicate the PNH clone, and must be given lifelong, it is best reserved for patients with prominent signs and symptoms of classical PNH. The author noted that, besides the original trials that led to the approval of eculizumab for treatment of PNH, not many other studies have been conducted to evaluate the long-term effects of eculizumab. The authors stated that more experience with administration of eculizumab should provide more evidence for clearer treatment parameters such as when to initiate treatment.

In a *Lancet* review of eculizumab for PNH, Parker (2009) explained the eculizumab does not increase the risk of catastrophic hemolytic crisis if the drug is discontinued. He noted that, of 195 patients in clinical trials, 16 had discontinued treatment with no catastrophic hemolysis reported. During treatment with eculizumab, the percentage of PNH erythrocytes in peripheral blood increases because eculizumab enhances survival of the abnormal cells by protecting them against complement-mediated lysis. The fact that treatment with eculizumab increases the proportion of these cells initially raised concerns that discontinuation of the drug might result in a hemolytic crisis. Parker (2009) reported, however, that 16 patients have discontinued treatment with eculizumab without having exacerbation of hemolysis. A more recent report by the Canadian Agency for Technology Assessment in Health (CADTH, 2010) also noted that, despite the theoretical possibility of a rebound effect upon discontinuation of eculizumab, no cases have been identified to date.

Eculizumab is also being examined in the treatment of various disorders/syndromes including antibody-mediated rejection, Guillain-Barre syndrome, hemolytic uremic syndrome, and systemic lupus erythematosus. However, there is currently insufficient evidence to support the use of eculizumab for most of these conditions.

van Doorn (2009) noted that epidemiological studies have shown that the incidence of Guillain-Barre syndrome (GBS) remains stable at about 2/100,000 per year; but that there have been changes in hospitalization use, likely due to the widespread availability of intravenous immunoglobulin (IVIG). Research into mechanisms has shown the
importance of single amino acids in Campylobacter jejuni and the importance of ganglioside conformation. In a murine model of anti-ganglioside antibody-mediated neuropathy, eculizumab was effective in reversing clinical disease and preventing pathology. This suggests trials of eculizumab in GBS should be considered. However, there are no new randomized controlled trials in GBS to report.

Robak and Robak (2009) stated that systemic lupus erythematosus (SLE) is an autoimmune disease characterized by B cell hyperactivity and defective T-cell function, with production of high titer auto-antibodies. In the recent years, conceptual advances and the introduction of new therapies are yielding improvements in the management of this disease; clinical studies have been undertaken with selected monoclonal antibodies (mAbs) in the treatment of SLE. The important role of B cells in the pathogenesis of autoimmune disorders has provided a strong rationale to target B cells in SLE. Selective therapeutic depletion of B-cells became possible with the availability of the anti-CD20 antibody rituximab and anti-CD22 antibody epratuzumab. Several clinical studies confirm high activity of rituximab in SLE patients especially with lupus nephritis and neuropsychiatric involvement. Recently, several new mAbs reacting with CD20 have been developed. New mAbs directed against CD20 include fully human mAb ofatumumab, which has a greater than 90 % humanized framework and GA-101, a novel third-generation fully humanized and optimized mAb. These agents are highly cytotoxic against B-cell lymphoid cells. Pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6 play an important role in propagating the inflammatory process responsible for tissue damage. Blocking of these cytokines by mAbs can be also a successful therapy for patients with SLE. Finally, mAb eculizumab that specifically inhibits terminal complement activation has been recently developed and investigated in the phase I single dose study in SLE.

Stegall and Gloor (2010) described recent studies regarding the mechanisms of antibody-mediated rejection (AMR) and new clinical protocols aimed at prevention and/or treatment of this difficult clinical entity. These investigators noted that the natural history of acute AMR after positive cross-match kidney transplantation involves an acute rise in donor-specific alloantibody in the first few weeks following transplantation. Whereas the exact cellular mechanisms responsible for AMR are not known, it seems likely that both pre-existing plasma cells and the conversion of memory B cells to new plasma cells play a role in the increased donor-specific alloantibody production. One recent study suggested that combination therapy with plasmapheresis, high-dose IVIG and rituximab was more effective treatment for AMR than high-dose IVIG alone, but the role of anti-CD20 antibody is still unclear. Two new promising approaches to AMR focus on depletion of plasma cells with bortezomib as well as the inhibition of terminal complement activation with eculizumab. The authors concluded that the pathogenesis of AMR in several different clinical settings is becoming clearer and more effective treatments are being developed. Whether the prevention or successful treatment of AMR will decrease the prevalence of chronic injury and improved long-term graft survival will require longer-term studies. Moreover, in a review on advances in diagnosing and managing AMR, Jordan et al (2010) stated that newer approaches in treating AMR include bortezomib and eculizumab.

Scheiring and associates (2010) stated that hemolytic uremic syndrome (HUS) entails the triad of hemolytic anemia, thrombocytopenia, and acute renal failure. The classical form [D(+) HUS] is caused by infectious agents, and it is a common cause of acute renal failure in children. The enterohemorrhagic Escherichia coli-producing Shiga toxin (Stx) is the most common infectious agent causing HUS. Other infectious agents are Shigella and
Streptococcus pneumoniae. Infections by Streptococcus pneumoniae can be severe and has a higher acute mortality and a higher long-term morbidity compared to HUS by Stx. Atypical HUS [D(-)Stx(-)HUS] are often used by pediatricians to indicate a presentation of HUS without preceding diarrhea. Almost all patients with D(-)Stx(-)HUS have a defect in the alternative pathway (e.g., mutations in the genes for complement factor H, factor I, and membrane co-factor protein). Mutations in the factor H gene are described more often. The majority of children with D(+) HUS develop some degree of renal insufficiency, and about 2/3 of children with HUS will require dialysis, while about 1/3 will have milder renal involvement without the need for dialysis. Standard treatment of acute renal failure includes appropriate fluid and electrolyte management, anti-hypertensive therapy, and the initiation of renal replacement therapy when appropriate. Specific management issues in HUS include treatment of the hematological complications of HUS, monitoring for extra-renal involvement, avoiding anti-diarrheal drugs, and possibly avoiding of antibiotic therapy. In addition to the obligatory supportive treatment and tight control of hypertension, there is anecdotal evidence that plasma therapy may induce remission and, in some cases, maintain it. Fresh frozen plasma contains factor H at physiological concentrations. A new therapy for D(-)Stx(-)HUS is eculizumab, which prevents the generation of the inflammatory peptide C5a and the cytotoxic membrane-attack complex C5b-9. These investigators noted that they have the first positive results. Furthermore, in a review on atypical HUS, Kavanagh and Goodship (2010) noted that although early reports of the effectiveness of eculizumab are promising, the outcome of a recent clinical trial is awaited. Waters and Licht (2011) stated that clinical trials are now underway to evaluate the effectiveness of eculizumab in the management of both plasma-sensitive and plasma-resistant atypical HUS.

Hemolytic uremic syndrome is defined by the triad of mechanical hemolytic anemia, thrombocytopenia and renal impairment. Atypical HUS (aHUS) defines non Shiga-toxin-HUS and even if some authors include secondary aHUS due to Streptococcus pneumoniae or other causes, aHUS designates a primary disease due to a disorder in complement alternative pathway regulation. Atypical HUS represents 5 to 10 % of HUS in children, but the majority of HUS in adults. The incidence of complement-aHUS is not known precisely. However, more than 1,000 aHUS patients investigated for complement abnormalities have been reported. Onset is from the neonatal period to the adult age. Most patients present with hemolytic anemia, thrombocytopenia and renal failure and 20 % have extra renal manifestations. Two to 10 % die and 1/3 progress to end-stage renal failure at first episode. Half of patients have relapses. Mutations in the genes encoding complement regulatory proteins factor H, membrane cofactor protein (MCP), factor I or thrombomodulin have been demonstrated in 20 to 30 %, 5 to 15 %, 4 to 10 % and 3 to 5 % of patients respectively, and mutations in the genes of C3 convertase proteins, C3 and factor B, in 2 to 10 % and 1 to 4 %. In addition, 6 to 10 % of patients have anti-factor H antibodies. Diagnosis of aHUS relies on (i) no associated disease, (ii) no criteria for Stx-HUS (stool culture and polymerase chain reaction for Stx; serology for anti-lipopolysaccharides antibodies), and (iii) no criteria for thrombotic thrombocytopenic purpura (serum ADAMTS 13 activity greater than 10 %). Investigation of the complement system is required (C3, C4, factor H and factor I plasma concentration, MCP expression on leukocytes and anti-factor H antibodies; genetic screening to identify risk factors). The disease is familial in approximately 20 % of pedigrees, with an autosomal recessive or dominant mode of transmission. As penetrance of the disease is 50 %, genetic counseling is difficult. Plasma therapy (plasma exchange or fresh frozen plasma infusion) has been first line treatment. Patients with aHUS who have reached end-stage renal
failure are theoretically candidates to renal transplantation. However, the overall risk of
aHUS recurrence after renal transplantation is 50 % and the risk of graft loss 80 to 90 % in
patients with recurrence. Case reports and 2 phase II trials suggested that the
complement C5 blocker eculizumab will be the next standard of care (Loirat and
Fremeaux-Bacchi, 2011).

Tschumi et al (2011) stated that the prognosis for patients with aHUS is poor, and plasma
exchange represents the first-line therapy. These investigators reported the case of a 9-year
old girl with frequent relapsing aHUS due to heterozygous factor H mutation who was
initially treated with plasma exchange 3 times per week with 150 % plasma exchange
volume. This treatment frequently caused allergic reactions and school absences.
Because any reduction in the frequency of plasma exchange immediately induced
relapses of the aHUS, treatment with eculizumab, 600 mg every 2 weeks, was started and
plasma exchange completely stopped. On this drug regimen the patient showed no
evidence of disease activity during a period of more than 24 months. Renal function
improved, proteinuria disappeared, the number of anti-hypertensive medications could be
decreased, and the quality of life increased substantially. The inhibition of the terminal
complement pathway by eculizumab was also confirmed by renal biopsy, which showed
the absence of thrombotic microangiopathy 2 months after the initiation of eculizumab
therapy. This case illustrated the long-term favorable outcome of aHUS with eculizumab
treatment.

Lapeyraque et al (2011) stated that the use of early-onset plasma therapy for aHUS is
recommended, but optimal long-term treatment regimen is not well-defined. Eculizumab
has shown success in patients with aHUS. These researchers reported a 7-year old girl
with aHUS associated with factor H mutations successfully treated with eculizumab.
Weekly plasma infusion (PI) of 25 to 30 ml/kg with short-term intensified PI during aHUS
exacerbations was effective for 4.3 years. Progressive mild renal failure (stage 2) was
attributed to chronic glomerular lesions. Subsequently, the patient exhibited aHUS
exacerbation unresponsive to intensified PI. Eculizumab was initiated at 600 mg, resulting
in immediate and complete inhibition of terminal complement activation. During the week
following treatment, these investigators observed a complete reversal of aHUS activity.
She has been receiving 600 mg eculizumab every 2 weeks for the last 12 months. She
had no aHUS exacerbation, and serum creatinine level returned to normal. In this patient,
eculizumab led to control of PI-resistant aHUS exacerbation and chronic microangiopathic
hemolytic activity. Clinical trials are ongoing to assess the safety and effectiveness of this
drug in the management of aHUS.

On September 23, 2011, the FDA approved eculizumab to treat patients with aHUS. The
safety and effectiveness of eculizumab for the treatment of aHUS were established in two
single-arm trials in 37 adults and adolescent patients with aHUS and one retrospective
study in 19 pediatric patients and 11 adult patients with aHUS. Patients treated with
eculizumab in these studies experienced a favorable improvement in renal function,
including elimination of the requirement for dialysis in several patients with aHUS that did
not respond to plasma therapy. Patients treated with eculizumab also exhibited
improvement in platelet counts and other blood parameters that correlate with aHUS
disease activity. The most common side effects observed in patients treated with
eculizumab for aHUS included anemia, diarrhea, headache, hypertension, leukopenia,
nausea, vomiting, as well as upper respiratory and urinary tract infections. This new
indication for eculizumab is being approved with an extension of the existing Risk
Evaluation and Mitigation Strategy (REMS), to inform health care professionals and
patients about the known risk of life-threatening meningococcal infections. Eculizumab is contraindicated in patients with unresolved serious Neisseria meningitidis infection.

McCaugan and associates (2012) stated that dense deposit disease is a rare glomerulonephritis caused by uncontrolled stimulation of the alternative complement pathway. Allograft survival after kidney transplantation is significantly reduced by the high rate of disease recurrence. No therapeutic interventions have consistently improved outcomes for patients with primary or recurrent disease. This was the first reported case of recurrent dense deposit disease being managed with eculizumab. Within 4 weeks of renal transplantation, deteriorating graft function and increasing proteinuria were evident. A transplant biopsy confirmed the diagnosis of recurrent dense deposit disease. Eculizumab was considered after the failure of corticosteroid, rituximab and plasmapheresis to attenuate the rate of decline in allograft function. There was a marked clinical and biochemical response following the administration of eculizumab. This case provided the first evidence that eculizumab may have a place in the management of crescentic dense deposit disease. The authors noted that more information is needed to clarify the effectiveness and role of eculizumab in dense deposit disease but the response in this patient was encouraging. The results of clinical trials of eculizumab in this condition are eagerly awaited.

In an open-label, proof of concept efficacy and safety study, Bomback et al (2012) examined the effects of eculizumab for dense deposit disease and C3 glomerulonephritis. A total of 6 subjects with dense deposit disease or C3 glomerulonephritis were treated with eculizumab every other week for 1 year. All had proteinuria greater than 1 g/day and/or AKI at enrollment. Subjects underwent biopsy before enrollment and repeat biopsy at the 1-year mark. The subjects included 3 patients with dense deposit disease (including 1 patient with recurrent dense deposit disease in allograft) and 3 patients with C3 glomerulonephritis (including 2 patients with recurrent C3 glomerulonephritis in allograft). Genetic and complement function testing revealed a mutation in CFH and MCP in 1 subject each, C3 nephritic factor in 3 subjects, and elevated levels of serum membrane attack complex in 3 subjects. After 12 months, 2 subjects showed significantly reduced serum creatinine, 1 subject achieved marked reduction in proteinuria, and 1 subject had stable laboratory parameters but histopathologic improvements. Elevated serum membrane attack complex levels normalized on therapy and paralleled improvements in creatinine and proteinuria. The authors concluded that clinical and histopathologic data suggest a response to eculizumab in some but not all subjects with dense deposit disease and C3 glomerulonephritis. Elevation of serum membrane attack complex before treatment may predict response. They stated that additional research is needed to define the subgroup of dense deposit disease/C3 glomerulonephritis patients in whom eculizumab therapy can be considered.

In a Cochrane review, Gordon and colleagues (2012) evaluated the effects of immunosuppressants and immunomodulatory treatments for dermatomyositis and polymyositis. These investigators searched the Cochrane Neuromuscular Disease Group Specialized Register (August 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 3 2011), MEDLINE (January 1966 to August 2011), EMBASE (January 1980 to August 2011) and clinicaltrials.gov (August 2011). They checked the bibliographies of identified trials and wrote to disease experts. These researchers included all randomized controlled trials (RCTs) or quasi-RCTs involving participants with probable or definite dermatomyositis and polymyositis as defined by the criteria of Bohan and Peter, or definite, probable or mild/early by the criteria of Dalakas. In
participants without a classical rash of dermatomyositis, inclusion body myositis should have been excluded by muscle biopsy. These investigators considered any immunosuppressant or immunomodulatory treatment. The 2 primary outcomes were the change in a function or disability scale measured as the proportion of participants improving 1 grade, 2 grades etc, pre-defined based on the scales used in the studies after at least 6 months, and a 15% or greater improvement in muscle strength compared with baseline after at least 6 months. Other outcomes were: the International Myositis Assessment and Clinical Studies Group (IMACS) definition of improvement, number of relapses and time to relapse, remission and time-to-remission, cumulative corticosteroid dose and serious adverse effects. Two authors independently selected papers, extracted data and assessed risk of bias in included studies. They collected adverse event data from the included studies. The review authors identified 14 relevant RCTs; they excluded 4 trials. The 10 included studies, 4 of which have been added in this update, included a total of 258 participants. Six studies compared an immunosuppressant or immunomodulator with placebo control, and 4 studies compared 2 immunosuppressant regimes with each other. Most of the studies were small (the largest had 62 participants) and many of the reports contained insufficient information to assess risk of bias. Amongst the 6 studies comparing immunosuppressant with placebo, 1 study, investigating IVIG, showed statistically significant improvement in scores of muscle strength in the IVIG group over 3 months. Another study investigating etanercept showed some evidence of a steroid-sparing effect, a secondary outcome in this review, but no improvement in other assessed outcomes. The other 4 randomized placebo-controlled trials assessed either plasma exchange and leukapheresis, eculizumab, infliximab or azathioprine against placebo and all produced negative results. Three of the 4 studies comparing 2 immunosuppressant regimes (azathioprine with methotrexate, ciclosporin with methotrexate, and intra-muscular methotrexate with oral methotrexate plus azathioprine) showed no statistically significant difference in efficacy between the treatment regimes. The 4th study comparing pulsed oral dexamethasone with daily oral prednisolone and found that the dexamethasone regime had a shorter median time to relapse but fewer side effects. Immunosuppressants were associated with significant side effects. The authors concluded that this systematic review highlighted the lack of high quality RCTs that evaluate the effectiveness and toxicity of immunosuppressants in inflammatory myositis.

Diaz-Manera et al (2012) noted that new treatments for immune mediated diseases have increased notably in the past decade. Monoclonal antibodies directed against different components of the immune system have appeared, along with new drugs from the hematology field. In the case of myasthenia gravis (MG), many of these new treatments have been used in experimental animal models and also in patients. These investigators reviewed the progress in the field of MG treatment achieved in the last 5 years. Firstly, the authors’ current treatment protocol was introduced. Secondly, new data from recent randomized trials and case series of patients treated with methotrexate, cyclophosphamide, rituximab or improved systems of apheresis was reported. Finally, all future treatments were discussed that are currently under evaluation in pre-clinical animal models of experimental autoimmune MG. Evidence supporting the use of methotrexate and rituximab in MG has been published recently, in addition to conflicting randomized trials that were not successful, evaluating the use of tacrolimus as a steroid sparing agent. New promising treatments are currently under evaluation in clinical trials, such as belimumab and eculizumab.
An UpToDate review on “Investigational immunosuppressive drugs and approaches in clinical kidney transplantation” (Vella, 2013) states that “Agents currently under development include eculizumab, alefacept, voclosporine, sotraustain, tasocitinib, and bortezomib. The roles for bortezomib and eculizumab in the management of antibody mediated rejection remain to be defined. All of the other agents discussed in this topic review either have had their development discontinued or remain in early phase clinical trials”.

Canaud et al (2013) stated that thrombotic microangiopathy (TMA) is one of the hallmark vascular lesions of anti-phospholipid syndrome nephropathy (APSN). These lesions are at high risk of recurrence after kidney transplantation. The complement pathway is thought to be active in this process. These researchers used eculizumab to treat 3 consecutive kidney transplant recipients with post-transplant TMA due to APSN recurrence that was resistant to plasmapheresis and explored the complement deposition and apoptotic and vascular cell markers on the sequential transplant biopsies. Treatment with eculizumab resulted in a rapid and dramatic improvement of the graft function in all 3 patients and in improvement of the TMA lesions within the graft. None of these patients had TMA flares after eculizumab was withdrawn. At the time of TMA diagnosis, immunofluorescence studies revealed intense C5b-9 and C4d depositions at the endothelial cell surface of the injured vessels. Moreover, C5b-9 co-localized with vessels exhibiting a high rate of apoptotic cells. Examination of sequential biopsies during eculizumab therapy showed that TMA lesions, C4d and apoptotic markers were rapidly cleared, but the C5b-9 deposits persisted for several months as a footprint of the TMA. Finally, these investigators noticed that complement inhibition did not prevent the development of the chronic vascular changes associated with APSN. They stated that eculizumab seems to be an efficient method for treating severe forms of post-transplant TMA due to APSN recurrence. Moreover, terminal complement inhibition does not prevent the development of chronic APSN.

Rovira and colleagues (2013) stated that immune hemolytic anemia is a well-recognized complication after allogeneic hematopoietic stem cell transplantation (HSCT). There are 4 possible causes for this complication: (i) antibodies present in the recipient destroy donor cells, (ii) donor red cell antibodies at the time of stem cell infusion are transferred to the recipient, (iii) sometimes, engrafted donor lymphocytes cause active production of red cell antibodies, and (iv) another cause of hemolysis after allogeneic HSCT is autoimmune hemolytic anemia (AIHA). It is thought to be due to antibodies produced by the donor’s immune system against antigens on red cells of donor origin. Autoimmune hemolytic anemia after allogeneic HSCT is rare, it is still not well-characterized, and it represents a life-threatening situation. These investigators described 2 patients with acute myeloid leukemia treated with intensive chemotherapy and umbilical cord blood stem cell transplantation (UCBT). One patient developed AIHA at day +182, and the other at day +212 after receiving UCBT. Patients received 5 and 7 line treatment options, respectively, including continuous corticosteroids, IVIG, splenectomy, cyclophosphamide, plasma exchange, rituximab, bortezomib, and eculizumab. However, both patients died because of massive hemolysis after 85 and 106 days of intensive treatment, respectively. These cases reflected the extreme difficulty in the therapeutic management of patients with AIHA following UCBT. The authors concluded that after an extensive review of the literature, the exact physiopathologic mechanisms of AIHA after allogeneic HSCT in general, and after UCBT in particular, and therefore an effective treatment remain unknown.
Nobile-Orazio and Gallia (2013) stated that multi-focal motor neuropathy (MMN) is a purely motor mononeuritis multiplex characterized by the presence of conduction block on motor but not on sensory nerves and by the presence of high titers of anti-GM1 antibodies. Several studies pointed to a pathogenetic role of the immune system in this neuropathy, although this has not yet been proved. Several uncontrolled studies and RCTs have demonstrated the efficacy of therapy with high-dose IVIG in MMN. However, this therapy has a short-lasting effect that needs to be maintained with periodic infusions. This can be partly overcome by the use of subcutaneous immunoglobulin (SCIG) at the same dose. The high cost and need for repeated infusions have led to the search for other immune therapies, the efficacy of which had not yet been confirmed in RCTs. In addition, some therapies, including corticosteroids and plasma exchange, are not only ineffective, but have been associated with clinical worsening. More recently, a number of novel therapies have been investigated in MMN, including interferon-β1a, rituximab, and eculizumab. Preliminary data from open-label uncontrolled studies showed that some patients improve after these therapies; however, RCTs are needed to confirm effectiveness.

Burwick and Feinberg (2013) noted that severe preeclampsia with hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome is a leading cause of maternal and neonatal morbidity and mortality worldwide. Occurrence at an extremely premature gestational age is most challenging as there are dichotomous imperatives: delivery as definitive therapy for maternal health versus prolongation of pregnancy to avoid prematurity and associated morbidities. These researchers described a patient presenting with severe preeclampsia/HELLP syndrome at 26 weeks gestation that was treated with eculizumab, which resulted in marked clinical improvement and complete normalization of laboratory parameters. Pregnancy was prolonged 17 days, likely resulting in a reduction of neonatal morbidity with its associated short- and long-term health care costs. The authors concluded that successful use of eculizumab in this case suggested that complement inhibition may be an effective treatment strategy for severe preeclampsia/HELLP syndrome. The finding of this single-case study needs to be validated by well-designed studies.

Fujihara (2012) stated that neuromyelitis optica (NMO) or Devic’s disease is an inflammatory neurologic disease characterized by severe optic neuritis and transverse myelitis. Other features of NMO include female preponderance, higher onset age, severe functional disability, longitudinally extensive spinal cord lesions (longer than 3 vertebral segments), and oligoclonal IgG bands negativity. Brain lesions are not uncommon in NMO. The relation between NMO and multiple sclerosis (MS) has long been a matter of controversy, but since the discovery of anti-aquaporin 4 (AQP4) antibody (NMO-IgG), an NMO-specific autoantibody, the clinical, MRI, and laboratory features that distinguish NMO from MS have been clarified. Anti-AQP4 antibody binds to the extracellular domain of AQP4, which is highly expressed in end-feet of astrocytes. Recent neuropathological studies, analysis of cerebrospinal fluid-glial fibrillary acidic protein (CSF-GFAP) levels during relapse and experimental studies strongly suggested that NMO is an anti-AQP4 antibody-mediated astrocytopathic disease and that T cell-mediated CNS inflammation is necessary to develop NMO. Also, interleukin-6 (IL-6) is remarkably elevated in the CSF and appears to regulate plasmablasts to produce anti-AQP4 antibody. Therefore, from the therapeutic point of view, depletion of anti-AQP4 antibody, suppression of T cell response to trigger relapse and anti-IL-6 therapy seemed to be pivotal. High-dose intravenous methylprednisolone is the first-line therapy for acute exacerbations of NMO.
But plasma exchange should be started soon if corticosteroid is not effective. If untreated, AQP4 antibody-positive patients are highly likely to experience relapses within a year. Therefore, immunosuppressive therapy (corticosteroids, immunosuppressants, rituximab) should be initiated without delay. Preliminary results suggested that eculizumab can also prevent relapse in NMO. Meanwhile, interferon-beta, a first-line disease modifying drug of MS, is ineffective in NMO. Moreover, symptomatic therapy for pain, paresthesia, spasticity, dysuria and constipation that commonly occur in the chronic stage of NMO is also important to improve patients’ quality of life.

In an open-label, pilot study, Pittock and associates (2013) examined the use of eculizumab in the treatment of NMO spectrum disorders. Between October 20, 2009, and November 3, 2010, these researchers recruited patients from 2 U.S. centers into an open-label trial. Patients were AQP4-IgG-seropositive, aged at least 18 years, had a NMO spectrum disorder, and had at least 2 attacks in the preceding 6 months or 3 in the previous 12 months. Patients received meningococcal vaccine at a screening visit and 2 weeks later began eculizumab treatment. They received 600-mg intravenous eculizumab weekly for 4 weeks, 900-mg in the 5th week, and then 900-mg every 2 weeks for 48 weeks. The co-primary end-points were efficacy (measured by number of attacks [new worsening of neurological function lasting for more than 24 hours and not attributable to an identifiable cause]) and safety. Secondary end-points were disability (measured by expanded disability status scale), ambulation (Hauser score), and visual acuity. At follow-up visits (after 6 weeks and 3, 6, 9, and 12 months of treatment; and 3 and 12 months after discontinuation), complete neurological examination was undertaken and an adverse event questionnaire completed. These investigators enrolled 14 patients, all of whom were women. After 12 months of eculizumab treatment, 12 patients were relapse-free; 2 had had possible attacks. The median number of attacks per year fell from 3 before treatment (range 2 to 4) to 0 (0 to 1) during treatment (p < 0.0001). No patient had worsened disability by any outcome measure. Median score on the expanded disability status scale improved from 4.3 (range 1.0 to 8.0) before treatment to 3.5 (0 to 8.0) during treatment (p = 0.0078). Two patients improved by 2 points and 3 improved by 1 point on the Hauser score; no change was recorded for the other patients. Visual acuity had improved in at least 1 eye by 1 point in 4 patients, and by 2 points in 1 patient; no change was recorded for other patients. One patient had meningococcal sepsis and sterile meningitis about 2 months after the first eculizumab infusion, but resumed treatment after full recovery. No other drug-related serious adverse events occurred. Eight attacks in five patients were reported within 12 months of eculizumab withdrawal. The authors concluded that eculizumab seems to be well-tolerated, significantly reduce attack frequency, and stabilize or improve neurological disability measures in patients with aggressive NMO spectrum disorders. Moreover, they stated that the apparent effects of eculizumab deserve further investigation in larger, RCTs.

Damico et al (2012) noted that emerging treatments for dry age-related macular degeneration (ARMD) and geographic atrophy focus on 2 strategies that target components involved in physiopathological pathways: (i) prevention of photoreceptors and retinal pigment epithelium loss (neuro-protection induction, oxidative damage prevention, and visual cycle modification), and (ii) suppression of inflammation. Neuro-protective drugs, such as ciliary neurotrophic factor, brimonidine tartrate, tandospirone, and anti-amyloid β antibodies, aim to prevent apoptosis of retinal cells. Oxidative stress and depletion of essential micronutrients are targeted by the Age-Related Eye Disease Study (AREDS) formulation. Visual cycle modulators reduce the activity of the photoreceptors and retinal accumulation of toxic fluorophores and lipofuscin. Eyes with
dry ARMD present chronic inflammation and potential treatments include corticosteroid and complement inhibition.

Leung and Landa (2013) stated that ARMD is the leading cause of irreversible blindness in developed countries. There are currently no cures, but there are promising potential therapies that target the underlying disease mechanisms of dry ARMD. Stem cells, ciliary neurotrophic factor, rheopheresis, ozonated auto-hemotherapy, as well as prostaglandins show promise in stabilizing or improving visual acuity; and AREDS vitamins may reduce progression to severe ARMD. Adjuvant therapy like low-vision rehabilitation and implantable miniature telescopes may help patients adjust to the sequelae of their disease, and herbal supplementation with saffron, zinc monocycteine and phototrop may be helpful. Therapies that are currently in clinical trials include brimonidine, doxycycline, anti-amyloid antibodies, complement inhibitors, hydroxychloroquine, intra-vitreal fluocinolone acetate and vasodilators (e.g., sildenafil and moxaverine). Therapies that have not been shown to be effective include POT-4, eculizumab, tandospirone, anecortave acetate, the antioxidant OT-551, sirolimus and vitamin E.

Orandi and colleagues (2014) stated that incompatible live donor kidney transplantation is associated with an increased rate of AMR and subsequent transplant glomerulopathy. For patients with severe, oliguric AMR, graft loss is inevitable without timely intervention. These investigators reviewed their experience rescuing kidney allografts with this severe AMR phenotype by using splenectomy alone (n = 14), eculizumab alone (n = 5), or splenectomy plus eculizumab (n = 5), in addition to plasmapheresis. The study population was 267 consecutive patients with donor-specific antibody undergoing desensitization. In the first 3 weeks after transplantation (median = 6 days), 24 patients developed sudden onset oliguria and rapidly rising serum creatinine with marked rebound of donor-specific antibody, and a biopsy that showed features of AMR. At a median follow-up of 533 days, 4 of 14 splenectomy-alone patients experienced graft loss (median = 320 days), compared to 4 of 5 eculizumab-alone patients with graft failure (median = 95 days). No patients treated with splenectomy plus eculizumab experienced graft loss. There was more chronic glomerulopathy in the splenectomy-alone and eculizumab-alone groups at 1 year, whereas splenectomy plus eculizumab patients had almost no transplant glomerulopathy. The authors concluded that these data suggested that for patients manifesting early severe AMR, splenectomy plus eculizumab may provide an effective intervention for rescuing and preserving allograft function. These preliminary findings need to be validated by well-designed studies.

In a prospective, double-masked, randomized clinical trial, Yehoshua et al (2014) evaluated the effect of eculizumab on the growth of geographic atrophy (GA) in patients with ARMD. Patients with GA measuring from 1.25 to 18 mm(2) based on spectral-domain optical coherence tomography (OCT) imaging were included in this study. Patients were randomized 2:1 to receive I.V. eculizumab or placebo over 6 months. In the eculizumab treatment-arm, the first 10 patients received a low-dose regimen of 600 mg weekly for 4 weeks followed by 900 mg every 2 weeks until week 24, and the next 10 patients received a high-dose regimen of 900 mg weekly for 4 weeks followed by 1,200 mg every 2 weeks until week 24. The placebo group was infused with saline. Patients were observed off treatment for an additional 26 weeks. Both normal-luminance and low-luminance visual acuities were measured throughout the study, and the low-luminance deficits were calculated as the difference between the letter scores. Main outcome measure was change in area of GA at 26 weeks. A total of 30 eyes of 30 patients were enrolled; 18 fellow eyes also met inclusion criteria and were analyzed as a secondary end-
point. For the 30 study eyes, mean square root of GA area measurements ± standard deviation at baseline were 2.55 ± 0.94 and 2.02 ± 0.74 mm in the eculizumab and placebo groups, respectively (p = 0.13). At 26 weeks, GA enlarged by a mean of 0.19 ± 0.12 and 0.18 ± 0.15 mm in the eculizumab and placebo groups, respectively (p = 0.96). At 52 weeks of follow-up, GA enlarged by a mean of 0.37 ± 0.22 mm in the eculizumab-treated eyes and by a mean of 0.37 ± 0.21 mm in the placebo group (p = 0.93, 2 sample t-test). None of the eyes converted to wet ARMD; no drug-related adverse events were identified. The authors concluded that systemic complement inhibition with eculizumab was well-tolerated through 6 months; but did not decrease the growth rate of GA significantly.

Vivarelli and Emma (2014) stated that C3 glomerulopathy (C3G) is a newly defined clinical entity comprising glomerular lesions with predominant C3 staining. Under this definition are now included membrano-proliferative glomerulonephritis type II (dense deposit disease) and C3 glomerulonephritis. This group of glomerular diseases with a heterogeneous histological aspect shares a common pathogenesis (i.e., a dysregulation of the alternative pathway of complement in the fluid phase leading to C3 deposition in the kidney). Recent advances have expanded the understanding of the underlying mechanisms, leading to the hypothesis that blocking the alternative complement pathway may be an effective treatment for C3Gs, as has been shown in other renal diseases driven by alternative pathway dysregulation, such as aHUS. Results of 11 published cases of patients with different forms of C3G treated with eculizumab are encouraging. The authors concluded that given the complexity of disease pathogenesis in C3G, a patient-tailored approach including a comprehensive workup of complement abnormalities is necessary to evaluate the best treatment options. Moreover, they stated that clinical trials assessing effectiveness of different complement blockers on the background of the individual complement profile are needed.

Tobin et al (2014) noted that longitudinally extensive transverse myelitis (LETM) is a frequently devastating clinical syndrome which has come into focus for its association with NMO. Recent advances in the diagnosis of NMO have led to very sensitive and specific tests and advances in therapy for this disorder. Longitudinally extensive transverse myelitis is not pathognomonic of NMO, therefore it is important to investigate for other causes of myelopathy in these patients. These researchers discussed recent advances in NMO diagnosis and treatment and the differential diagnosis in patients presenting with LETM. Fluorescence-activated cell sorting and cell binding assays for NMO-IgG are the most sensitive for detecting NMO spectrum disorders. Patients who have a clinical presentation of NMO, who have been tested with older ELISA or immunofluorescence assay and been found to be negative, should be re-tested with a fluorescence-activated cell sorting assay when available, particularly in the presence of recurrent LETM. The authors stated that novel therapeutic strategies for LETM in the context of NMO include eculizumab, which could be considered in patients with active disease who have failed azathioprine and rituximab. Moreover, they noted that thorough investigation of patients with LETM who are negative for NMO-IgG may lead to an alternate cause for myelopathy.

Rosenblad et al (2014) noted that immunoglobulin A (IgA) nephropathy is a chronic glomerulonephritis with excessive glomerular deposition of IgA1, C3 and C5b-9, which may lead to renal failure. These researchers described the clinical course of an adolescent with rapidly progressive disease leading to renal failure in spite of immunosuppressive treatment. Due to refractory disease the patient was treated with eculizumab (anti-C5) for 3 months in an attempt to rescue renal function. Treatment led to
clinical improvement with stabilization of the glomerular filtration rate (GFR) and reduced proteinuria. Discontinuation of treatment led to a rapid deterioration of renal function. This was followed by a single dose of eculizumab, which again reduced creatinine levels temporarily. The authors concluded that early initiation of eculizumab therapy in patients with progressive IgA nephropathy may have a beneficial effect by blocking complement-mediated renal inflammation. These preliminary findings need to be validated by well-designed studies.

The administration of eculizumab does not require concurrent vitamin B12 administration in persons without concurrent vitamin B12 deficiency. The Product Insert of Soliris (eculizumab) does not mention the use of vitamin B12 supplementation. [http://soliris.net/sites/default/files/assets/soliris_pi.pdf](http://soliris.net/sites/default/files/assets/soliris_pi.pdf).

Eculizumab is contraindicated in persons with unresolved serious *Neisseria meningitidis* infections, and in persons who are not currently vaccinated against *Neisseria meningitidis*.

The most commonly reported side effects associated with the use of eculizumab include anemia, back pain, cough, fatigue, headache, nasopharyngitis, nausea, pyrexia, and viral Infection.

**Appendix**

Recommended dosage of eculizumab for paroxysmal nocturnal hemoglobinuria:

- 600 mg IV every 7 days for the first 4 weeks, followed by
- 900 mg IV for the fifth dose 7 days later, then
- 900 mg IV every 14 days thereafter.

Recommended dosage of eculizumab for atypical hemolytic uremic syndrome (for patients 18 years of age or older):

- 900 mg IV every 7 days for the first 4 weeks, followed by
- 1,200 mg IV for the fifth dose 7 days later, then
- 1,200 mg IV every 14 days thereafter.

Recommended dosage of eculizumab for atypical hemolytic uremic syndrome (for patients less than 18 years of age; eculizumab is administered based on body weight):

<table>
<thead>
<tr>
<th>Patient body Weight</th>
<th>Induction</th>
<th>Maintenance</th>
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<tbody>
<tr>
<td>40 kg and over</td>
<td>900 mg weekly x 4 doses</td>
<td>1,200 mg at week 5; then 1,200 mg every 2 weeks</td>
</tr>
<tr>
<td>30 kg to &lt; 40 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>900 mg at week 3; then 900 mg every 2 weeks</td>
</tr>
<tr>
<td>Weight Range</td>
<td>Dosing Protocol</td>
<td>Schedule</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------</td>
<td>----------</td>
</tr>
<tr>
<td>20 kg to &lt; 30 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>600 mg at week 3; then 600 mg every 2 weeks</td>
</tr>
<tr>
<td>10 kg to &lt; 20 kg</td>
<td>600 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 2 weeks</td>
</tr>
<tr>
<td>5 kg to &lt; 10 kg</td>
<td>300 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 3 weeks</td>
</tr>
</tbody>
</table>

**Major Adverse Vascular Events (MAVE):**

**Venous thrombosis**
- Acute peripheral vascular occlusion,
- Clinically apparent distal embolization (e.g., lower extremity ulceration, tissue necrosis, gangrene, limb amputation or other end-organ damage)
- Deep vein thrombosis,
- Hepatic/portal vein thrombosis,
- Mesenteric/splenic vein thrombosis,
- Pulmonary embolus,
- Renal vein thrombosis,
- Thrombophlebitis.

**Arterial thrombosis**
- Cerebrovascular accident,
- Myocardial infarction,
- Transient ischemic attack,
- Unstable angina.

**Criteria for Diagnosis of Severe Aplastic Anemia:**

The diagnostic criteria for severe aplastic anemia are:

- A bone marrow biopsy showing less than 25 percent of normal cellularity; or a bone marrow biopsy showing less than 50 percent normal cellularity in which fewer than 30 percent of the cells are hematopoietic; and
- At least two of the following are present: 1) absolute reticulocyte count less than 40,000/microliter; 2) absolute neutrophil count (ANC) less than 500/microliter; or 3) platelet count less than 20,000/microliter.

Source: Guinan, 2011.
Eculizumab (Soliris)

96413 - 96417  Chemotherapy administration, intravenous infusion technique

**HCPCS codes covered if selection criteria are met:**

J1300  Injection, eculizumab, 10 mg

**ICD-9 codes covered if selection criteria are met:**

283.11  Hemolytic-uremic syndrome [covered for persons without serious unresolved Neisseria meningitis infection] [not covered for Shiga toxin E. coli-related hemolytic uremic syndrome(STEC-HUS)]

283.2  Hemoglobinuria due to hemolysis from external causes [paroxysmal nocturnal hemoglobinuria (PNH)]

**ICD-9 codes not covered for indications listed in the CPB (not an all inclusive list):**

283.0  Autoimmune hemolytic anemias

284.81 - 284.9  Other specified aplastic anemias [severe]

286.53  Antiphospholipid antibody with hemorrhagic disorder

341.0  Neuromyelitis optica [Devic’s disease]

357.0  Acute infective polyneuritis

357.82  Critical illness polyneuropathy [multi-focal motor neuropathy]

362.51  Nonexudative senile macular degeneration of retina

378.71  Duane’s syndrome [Turks syndrome]

446.0  Polyarteritis nodosa and allied conditions [Micro Polyangiitis]

446.4  Wegener’s granuloma

583.0 - 583.9  Nephritis and nephropathy, not specified as acute or chronic [deposit disease/C3 glomerulonephritis]

642.50 - 642.54  Severe pre-eclampsia [HELLP syndrome]

710.0  Systemic lupus erythematosus

710.3  Dermatomyositis

710.4  Polymyositis

729.1  Myalgia and myositis, unspecified [inflammatory myositis]

996.80 - 996.89  Complications of transplanted organ [antibody-mediated rejection]

**Other ICD-9 codes related to the CPB:**

036.0  Meningococcal meningitis [Neisseria]
041.41  Shiga toxin-producing E. coli
041.42  Other specified Shiga toxin-producing E. coli
041.43  Shiga toxin-producing E. coli, unspecified

287.30 - 287.5  Thrombocytopenia

V12.51  Personal history of venous thrombosis and embolism
V12.52  Personal history of thrombophlebitis
V12.54  Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits

The above policy is based on the following references:


51. Vella J. Investigational immunosuppressive drugs and approaches in clinical kidney transplantation. Last reviewed August 2013. UpToDate Inc., Waltham, MA.
